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Effects of the long acting β_2 agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids

T van der Molen, D S Postma, M O Turner, B Meyboom-de Jong, J L Malo, K Chapman, R Grossman, C S de Graaff, R A Riemersma, M R Sears, on behalf of The Netherlands and Canadian formoterol study investigators

Abstract

Background – The long acting β_2 agonist formoterol has proved to be an effective bronchodilator with a prolonged action of 12–14 hours. However, the precise role of formoterol in the maintenance treatment of asthma is still under debate. A study was performed to investigate the efficacy and safety of treatment with formoterol for six months in subjects with asthma.

Methods – In a multicentre double blind, placebo controlled, parallel group study 239 subjects with mild to moderate asthma were randomly assigned to treatment with either inhaled formoterol 24 μ g twice daily (n=125) or placebo (n=114) during eight months. The study consisted of a four week run in period, a 24 week treatment period, and a four week washout period. All subjects were using regular inhaled corticosteroids (100–3200 μ g daily) but were still needing at least five inhalations of short acting β_2 agonist per week for symptom relief. The study was performed in 10 outpatient clinics in Canada, and five outpatient clinics and one coordinating centre for 44 Dutch general practitioners in The Netherlands. Twice daily self-reported peak expiratory flow (PEF) measurements, symptom scores, and rescue β_2 agonist use during the last 28 treatment days compared with baseline values were used as main outcome measures. Spirometric values were measured at entry, at the start of treatment, after four, 12 and 24 weeks of treatment, and after four weeks washout.

Results – One hundred and twenty five subjects received formoterol 24 μ g twice daily via Turbohaler and 114 received placebo. Baseline FEV₁ was 67.1% predicted and mean bronchodilator reversibility was 26%. The mean total asthma symptom score was 3.6 (maximum possible 21). A significant decrease in symptoms in favour of formoterol (difference from placebo –0.64, 95% CI –0.04 to –1.23, p=0.04) was observed. Compared with placebo, morning PEF increased (difference from placebo 28 l/min, 95% CI 18.3 to 37.7, p=0.0001) and the use of short acting β_2 agonists decreased (daytime difference from placebo –1.1 inhalation, 95% CI –1.4 to –0.7, p=0.0001) in the

formoterol group. PEF returned to baseline following discontinuation of formoterol, as did asthma symptom scores. Thirty three patients treated with formoterol and 32 treated with placebo required treatment with prednisolone during the study (58 and 55 courses, respectively). **Conclusions** – Adding formoterol 24 μ g twice daily by Turbohaler to inhaled corticosteroids was effective in improving symptom scores and morning PEF, and decreasing the use of rescue β_2 agonists. There was no apparent loss of asthma control during 24 weeks of treatment with formoterol.

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Keywords: formoterol, long acting β_2 agonists, asthma, inhaled corticosteroids.

Inhaled β_2 adrenoceptor agonists are the most frequently used treatment in mild asthma and are of crucial importance in the treatment of acute bronchoconstriction.¹ However, their role in chronic maintenance treatment is controversial due to limited efficacy and has even caused some concern. Several studies have shown a decrease in control of symptoms or a more rapid deterioration of lung function associated with regular use of β_2 agonists as opposed to “if needed” treatment.^{2–4} Other studies have also reported mild tachyphylaxis to continuous β_2 agonist therapy but the changes were small and of doubtful clinical significance.^{5,6} The poor efficacy of maintenance treatment with short acting β_2 agonists compared with “if needed” treatment does not seem to be influenced by anti-inflammatory treatment with inhaled corticosteroids.⁷ There is no evidence that these concerns and the limited efficacy of maintenance treatment with short acting β_2 agonists apply also to long acting β_2 agonists. Since the use of a long acting bronchodilator provides “regular” treatment, it is important to investigate the efficacy and safety of maintenance treatment with long acting β_2 agonists in a sufficient number of subjects over a prolonged period.

We have undertaken a multicentre, long term, placebo controlled study on the effects of the long acting β_2 agonist formoterol in asthmatic subjects already using inhaled corticosteroids. The aim of the study was to assess the effect of regular formoterol on asthma

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Table 1 Mean (SD) characteristics of the patients in the formoterol and placebo groups at the beginning of the run-in period

	Formoterol (n = 125)	Placebo (n = 114)
Age (years)	40.5 (13.7)	45.4 (14.0)
Male (%)	48.8	49.2
Atopy (%)	68.8	66.6
Current smoking (n)	18	12
Smoking (pack years)	10.1 (7.1)	8.1 (4.1)
FEV ₁ (l)	2.29 (0.7)	2.16 (0.8)
(% predicted)	68 (15)	66 (16)
Post bronchodilator FEV ₁ (l)	2.85 (0.8)	2.69 (0.9)
Reversibility (% baseline)	25.2 (11.8)	26.3 (13.1)
Run-in values		
PEF morning (l/min)	392 (99.3)	382 (101.4)
PEF evening (l/min)	412 (97.7)	406 (97.5)
Symptom score total (max 21)	3.7 (2.8)	3.6 (3.0)
Rescue inhalations during day	2.4 (1.9)	2.0 (1.4)
Rescue inhalations during night	1.4 (1.2)	1.4 (0.9)
Dose of inhaled steroid (n)*		
≤ 400 µg	23	22
401–800 µg	28	19
801–1600 µg	51	48
≥ 1600 µg	20	24

FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow.

*Doses are expressed as equipotent doses. Four patients were not classified because they were using irregular doses.

control as judged by daily peak flow measurements, symptom scores, and frequency of exacerbations.

Methods

SUBJECTS

Two hundred and thirty nine adult asthmatic subjects (table 1) were studied for eight months (six months of treatment). The study was performed from June 1992 until October 1994 at 16 centres, six in The Netherlands and 10 in Canada. Sixty five subjects in The Netherlands were recruited from 44 general practitioners to a coordinating centre and 45 from five outpatient hospital clinics. All 129 subjects in Canada were recruited from 10 outpatient hospital clinics.

Inclusion criteria were asthma according to the definition of the American Thoracic Society,⁸ regular use of any dose of inhaled corticosteroids, the use of at least five inhalations of a short acting β_2 agonist per week before the entry visit, and >15% reversibility in baseline forced expiratory volume in one second (FEV₁) after two inhalations of 250 µg terbutaline (Bricanyl Turbhaler, Astra Draco, Sweden) or the equivalent dose of salbutamol. Exclusion criteria were the use of oral corticosteroids at any time in the last month, smoking history of >20 pack years, FEV₁ of <40% predicted, or an exacerbation of asthma symptoms during the previous month. The use of cromoglycate, theophylline, and anticholinergic drugs was not allowed during the study.

The study protocol was approved by the medical ethics committees of all participating centres. All subjects gave written informed consent.

STUDY DESIGN

A double blind, placebo controlled, parallel design was used with a run-in period of four weeks to obtain baseline values, a treatment period of 24 weeks, and a washout period of four weeks. The dose of inhaled corticosteroids

taken on entry was kept constant throughout the study. Terbutaline (250 µg inhalations via Turbhaler) was allowed as needed for relief of symptoms. No long acting β_2 agonists were allowed with the exception of the study medication. Theophyllines were stopped at least four days before the first visit.

At the end of the run-in period at the second visit subjects were randomly assigned to receive either formoterol (two inhalations of 12 µg twice daily) or placebo via a dry powder inhaler (Turbhaler). Randomisation was performed in blocks of four to one of the two treatment groups of equal size. Subjects came to the clinic on six occasions: on entry, after the four week run-in period, at weeks four, 12 and 24 of the treatment period, and after the four week washout period. Subjects were instructed not to take their morning dose of formoterol or placebo, and not to use supplemental terbutaline for six hours before clinic visits.

At each visit (and at the same time for each subject), FEV₁, blood pressure, and pulse rate were measured, and questions about adverse events were asked. The primary variable in the study was the total daily score of asthma symptoms. Subjects therefore filled in daily diary cards to record daytime symptoms of chest discomfort, sputum production, cough, activity, and wheezing on a scale ranging from 0 = none to 3 = very severe. Night time symptoms of wheeze and cough were recorded on the same scale adding up to a total asthma symptom score of 21. From previous studies of similar design it was estimated that, with 100 patients in each treatment group, there was an 80% chance of detecting a true mean difference of about 1.6 units in the change in score between the two treatment groups when using a test at the 5% significance level. This was based on the assumption that the standard deviation of the change for the total score was about 4 units. The highest of three measurements of peak expiratory flow (PEF) by mini-Wright peak flow meter was recorded each morning and evening, together with use of day and night time bronchodilators and other medication. PEF was measured before inhalation of the study drug, and the subjects were asked to refrain from the use of terbutaline at least six hours before a measurement. If there was a 20% drop from run-in values in morning PEF during two consecutive days, the subject telephoned the investigator who then initiated an oral prednisolone course for treatment of the exacerbation. All lung function measurements were made between 08.00 and 12.00 hours. β_2 agonists were stopped at least six hours before each test. FEV₁ was measured with a calibrated spirometer according to standardised guidelines.⁹ At least three reproducible values (<5% difference) were obtained and the highest value was used in the analyses.

ANALYSIS OF DATA

The primary variables of investigation were total asthma symptom score (sum of seven items; minimum score 0, maximum score 21) and morning PEF recorded in diaries. PEF was

Table 2 Reasons for discontinuation during treatment period

	Placebo	Formoterol
Asthma deterioration	6	1
Adverse event	1	5
Non-compliance	2	4
Unspecified reasons	4	8
Total	13	18

measured 12 hours after the last intake of study drug, thus reflecting the remaining effect of formoterol. Daily means, where missing data were substituted according to the last value extended principle, were used to illustrate the lung function and asthma symptoms during the entire study. The primary end point was the change from the run-in period (mean value over the last 14 days) to the end of the treatment period (mean value over the last 28 days). Comparisons of the treatments were performed using an analysis of variance model with the factors treatment and centre. Run-in values were used as covariates. The "all patients treated" approach was applied. A significance level of 5% was used.

Results

Two hundred and eighty subjects entered the run-in period of the study, and 239 subjects were randomised to two parallel treatment groups. Those receiving formoterol 24 µg twice daily ($n=125$) and placebo ($n=114$) had similar characteristics (table 1). The mean age of the subjects was 42.8 years and the duration of asthma was 20.6 years. Mean pre-bronchodilator FEV₁ was 67.1% of predicted normal, and mean reversibility was 25.7% at baseline. The dose of inhaled corticosteroids ranged from 100 µg to 3200 µg daily. Many kinds of

steroids were used and the doses are expressed in equipotent doses. Ninety two (38.5%) subjects used less than 800 µg, 99 (41.4%) used 800–1600 µg, and 44 (18.4%) used more than 1600 µg of any kind of inhaled corticosteroid daily. Despite instructions to the contrary, four subjects varied their dosage of inhaled corticosteroid.

Two hundred and eight subjects completed the study. Thirteen subjects using placebo and 18 subjects using formoterol discontinued treatment (table 2). Discontinuation due to deterioration of asthma was higher in the placebo group ($n=6$) than in the formoterol group ($n=1$). Discontinuation due to adverse events in the formoterol group ($n=5$) was caused by tremor (3), bronchospasm (1), and rash (1).

SYMPTOM SCORES

Results of the total symptom scores are presented in fig 1. In the formoterol group a small but statistically significant reduction in total symptom score occurred (difference between end of run-in period and end of treatment = 1.28) which lasted the whole treatment period and returned to baseline values immediately after the start of the washout period (difference between run-in and washout periods = 0.2). The placebo group reported a smaller change in symptom scores (0.64). The difference in the change in symptom scores between the two groups (0.64) was significant ($p=0.039$; 95% CI 1.23 to 0.04) and largely reflected changes in wheeze at night and chest discomfort. Both of these scores changed from 0.6 (last 14 days in run-in period) to 0.3 (last 28 days of treatment period) in the formoterol group, whereas the placebo group showed no difference. The mean (SD) change in the total symptom score during treatment with formoterol was -1.6 (2.6) in the low dose steroid group (≤ 400 µg) and -1.1 (2.9) in the high dose steroid group (≥ 1600 µg).

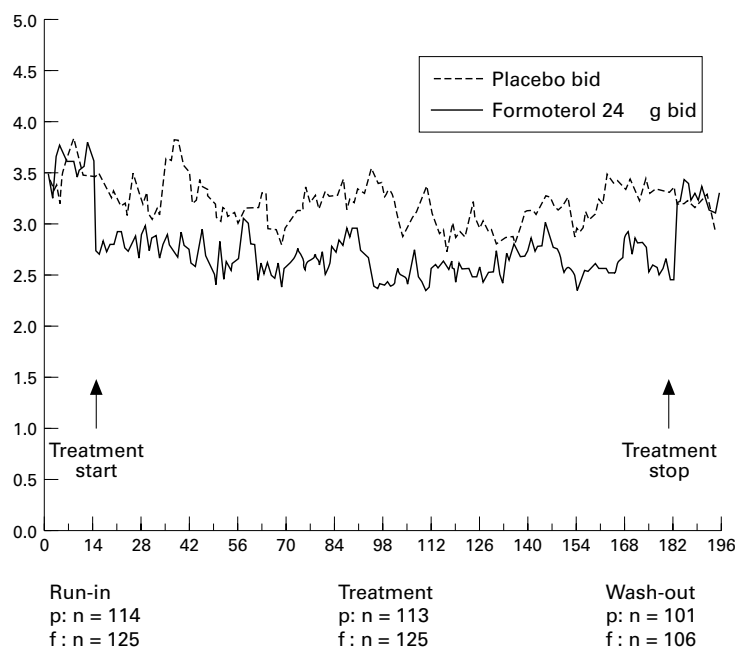


Figure 1 Daily mean total symptom scores before, during, and after treatment with formoterol or placebo.

PEAK FLOW (PEF)

Mean morning and evening PEF during the study are shown in fig 2. The mean changes in morning and evening PEF values from the last two weeks of the run-in period to the last four weeks of the treatment period were 25.9 l/min (morning) and 21.2 l/min (evening) in the formoterol group and -2.1 l/min (morning) and -5.9 l/min (evening) in the placebo group. The mean difference between the two groups was highly significant (morning PEF 28.1 (95% CI 18 to 38), $p<0.001$; evening PEF 27.1 (95% CI 17 to 37), $p<0.001$) and remained stable during the 24 weeks of treatment. Mean (SD) morning peak flow in the formoterol group was 391.6 (99.3) l in the last 14 days of the run-in period, and 393.4 (107.1) l in the washout period. Placebo values were 382.0 (101.4) l and 383.9 (103.5) l, respectively. The mean improvement in morning peak flow in the formoterol group was independent of the dose of inhaled steroid (≤ 400 µg, 31.3 l; ≥ 1600 µg, 32.8 l), the difference being not statistically significant ($p=0.55$).

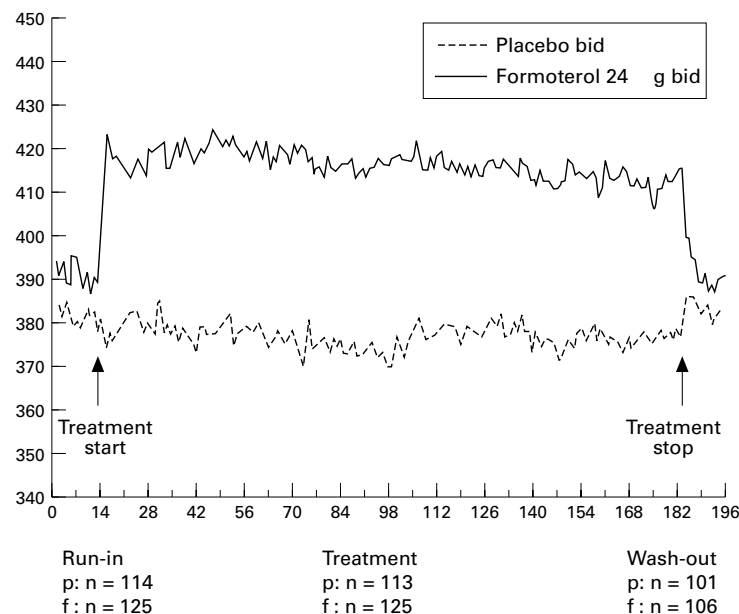


Figure 2 Daily mean morning peak flow values before, during, and after treatment with formoterol or placebo.

FEV₁

Mean (SD) FEV₁ at the start of the treatment period was 2.38 (0.77) l in the formoterol group and 2.21 (0.79) l in the placebo group. The mean FEV₁ in the formoterol group changed from 2.38 l at baseline to 2.57 (0.85) l after four weeks of treatment and to 2.51 (0.85) l after 24 weeks of treatment. In the placebo group the mean FEV₁ changed from 2.21 (0.79) l to 2.26 (0.82) l after four weeks of treatment and to 2.25 (0.84) l at the end of the treatment period. The change in FEV₁ from baseline was consistently larger with formoterol than placebo, the difference in the change between the groups being 0.18 l (95% CI 0.08 to 0.28) at week 8, 0.11 l (95% CI 0.00 to 0.21) at week 16, and 0.12 l (95% CI 0.02 to 0.22) at week 28. At the end of the washout period (week 32) there was no difference in the FEV₁ between the two groups. There were no indications of a difference in FEV₁ over time between the two treatment groups ($p=0.21$).

RESCUE MEDICATION

The mean daytime use of rescue medication (terbutaline 250 µg) in the formoterol treatment group decreased by 1.5 inhalations from run-in (mean 2.4) to treatment (mean 0.9) and returned to baseline values after the beginning of the washout period (mean 2.2). Mean night time rescue medication use decreased by 0.9 inhalations from 1.5 to 0.6 with a smaller decrease in the placebo group (−0.4 and −0.2, respectively). The difference between the two groups was highly significant (daytime −1.1 (95% CI −1.4 to −0.7), $p<0.001$; night time −0.8 (95% CI −1.0 to −0.5), $p<0.001$) and remained stable throughout the treatment period.

ASTHMA EXACERBATIONS

The number of courses of oral prednisolone used during the treatment period provided an indication of the total number of asthma exacerbations. Thirty two (28.1%) of the 114 subjects in the placebo group had 55 prednisolone courses and 33 (26.4%) of the 125 subjects in the formoterol group had 58 courses. The difference between the two groups was not statistically significant.

Discussion

The effect of adding inhaled formoterol, 24 µg twice daily, to inhaled corticosteroids in the treatment of asthmatic subjects was superior to placebo. Subjects treated with formoterol improved according to every variable in the study (daily symptom scores, PEF, requirement of additional bronchodilator use for symptom relief, and FEV₁) independently of steroid dose. The reported effects on PEF and FEV₁ were measured 12 hours after the intake of formoterol and are therefore minimum effects. Although desensitisation of β_2 receptors leading to a reduction in response would be noticed first on these effects, we did not find a reduction in response in any of the clinical variables tested, nor a worsening of asthma during the six months of treatment with formoterol. The mean difference in symptom scores between formoterol and placebo remained small but stable. Only six subjects discontinued the study because of asthma deterioration, five of them in the placebo group.

These results are consistent with the benefits seen in several other long term studies with long acting β_2 agonists.¹⁰⁻¹³ None of the studies has shown substantive evidence that treatment with long acting β_2 agonists has deleterious effects on asthma control. The available long term studies show maintenance of a constant bronchodilating effect and symptom control. In a multicentre study with 301 subjects Hekking *et al*¹³ compared formoterol (12 µg inhalation twice daily) with salbutamol (200 µg inhalation four times daily) for 12 weeks. The mean morning PEF in the formoterol group was 37 l/min higher than in the salbutamol group, and the mean numbers of recorded asthma attacks per week were 1.7 and 2.8, respectively, the difference being statistically significant. In another study by Kesten and co-workers¹⁴ inhaled formoterol in a dose of 12 µg twice daily provided better symptomatic control of asthma accompanied by reduced diurnal variation in PEF than inhaled salbutamol in a dose of 200 µg four times daily in a three month double blind study. In a 12 month follow up study the improvements in asthma control and lung function were maintained at the levels reached in the three month study.¹¹ Studies with another long acting β_2 agonist, salmeterol, reported similar findings.^{15,16} A recent report on the effects of added salmeterol in subjects already treated with inhaled corticosteroids¹⁰ showed better symptom control and higher mean morning and evening PEF in the salmeterol treated group than in the group treated with increased doses of corticosteroids. In a

12 month comparison between salmeterol and salbutamol Britton *et al*¹⁷ showed a clear improvement in PEF and symptom scores in the salmeterol group. The mean difference in improvement in morning PEF between the groups in their study was 30 l/min, slightly more than the 26 l/min reported here. However, formal comparisons of studies with salmeterol and formoterol to address the issue of whether the drugs have different efficacies is not possible. The inclusion criteria in the two studies were different so the results were being assessed in asthma of different severity. Further studies are needed to establish whether these drugs have a similar effectiveness.

In contrast to the studies with long acting β_2 agonists, regular treatment with short acting β_2 agonists has shown deleterious effects in some studies. Kraan *et al*¹⁸ suggested that an increase in airway hyperresponsiveness occurred with regular use of inhaled short acting β_2 agonists, while the converse was true among subjects taking inhaled corticosteroids. In other studies reporting the negative effects of regular short acting β_2 agonist therapy the detrimental effect seems not to be affected by inhaled corticosteroids.⁷ However, no deleterious effects were seen in our study when formoterol was added to inhaled corticosteroids for a period of six months. This was true for side effects, numbers of exacerbations, additional use of bronchodilators, and lung function variables. The present study, which is the first double blind study with a period of observation lasting six months, therefore suggests that formoterol is a safe drug when used with inhaled corticosteroids.

In summary, inhaled formoterol fumarate in a dose of 24 μ g twice daily is an effective long acting β_2 agonist that provides sustained improvement in asthma symptoms and objective measures of lung function during prolonged maintenance treatment in subjects who were also using inhaled corticosteroids. The efficacy was maintained throughout the treatment period. Although the place of long acting β_2 agonists in the management of asthma is still under discussion, our results suggest that regular treatment with long acting β_2 agonists in conjunction with inhaled corticosteroids is safe and often helpful.

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- 1 Barnes PJ. A new approach to the treatment of asthma. *N Engl J Med* 1989;321:1517-27.
- 2 van Schayck CP, Dompeling E, van Herwaarden CLA, Folgering H, Verbeek ALM, van der Hoogen HJM, *et al*. Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomised controlled study. *BMJ* 1991;303:1426-31.
- 3 Wahedna I, Wong CS, Wisniewski AFZ, Pavord ID, Tattersfield AE. Asthma control during and after cessation of regular beta₂-agonist treatment. *Am Rev Respir Dis* 1993;148:707-12.
- 4 Sears MR, Taylor DR. The β_2 -agonist controversy. Observations, explanations, and relationship to asthma epidemiology. *Drug Safety* 1994;2:259-83.
- 5 O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the non-bronchodilator effects of inhaled beta₂-agonists in asthma. *N Engl J Med* 1992;327:1204-8.
- 6 Dompeling E, van Schayck CP, van Grunsven PM, van Herwaarden CLA, Akkermans R, Molema J, *et al*. Slowing the deterioration of asthma and chronic obstructive pulmonary disease observed during bronchodilator therapy by adding inhaled corticosteroids. A 4 year prospective study. *Ann Intern Med* 1993;118:770-8.
- 7 Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Flannery EM, *et al*. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.
- 8 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
- 9 Quanjer PH. Standardized lung function testing. *Bull Eur Physiopathol Respir* 1983;19(Suppl 5):1-95.
- 10 Greening AP, Ind PW, Northfield M, Shaw G, Allen & Hanburys Limited UK Study Group. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344:219-24.
- 11 Kesten S, Chapman KR, Broder I, Cartier A, Hyland RH, Knight A, *et al*. Sustained improvement in asthma with long term use of formoterol fumarate. *Ann Allergy* 1992;69:415-20.
- 12 Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034-7.
- 13 Hekking PR, Maesen F, Greefhorst A, Prins J, Tan I, Zweers P. Long-term efficacy of formoterol compared to salbutamol. *Lung* 1990;Suppl:76-82.
- 14 Kesten S, Chapman KR, Broder I, Cartier A, Hyland RH, Knight A, *et al*. A three-month comparison of twice daily inhaled formoterol versus four times daily inhaled albuterol in the management of stable asthma. *Am Rev Respir Dis* 1991;144:622-5.
- 15 Ullman A, Hedner J, Svedmyr N. Inhaled salmeterol and salbutamol in asthmatic patients. *Am Rev Respir Dis* 1990;142:571-5.
- 16 Lötvall J, Lunde H, Ullman A, Törnqvist H, Svedmyr N. Twelve months, treatment with inhaled salmeterol in asthmatic patients: effects on beta₂-receptor in asthmatic patients. *Allergy* 1992;47:477-83.
- 17 Britton MG, Earnshaw JS, Palmer JB. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. *Eur Respir J* 1992;5:1062-7.
- 18 Kraan J, Koëter GH, van der Mark ThW, Sluiter HJ, de Vries K. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. *J Allergy Clin Immunol* 1985;76:628-36.